The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol Template (for Investigator Initiated Studies)

Title: Antibiotic Prophylaxis for Neonatal Abdominal Surgery: Defining the Optimal Dosing Regimen

1. Introduction and Purpose:

The purpose of this project will be to determine the optimal peri-operative antibiotic prophylaxis regimen for neonates undergoing general surgery procedures.

2. Background:

The optimal dosing regimen for surgical antibiotic prophylaxis in neonates undergoing general surgery procedures remains undefined. While multiple guidelines for surgical antibiotic prophylaxis have been published, these guidelines have been validated only through studies of adult patients [1]. Controversy therefore persists in applying these guidelines to the pediatric population as a whole. Concerns are heightened in the neonatal subgroup. Infants in the neonatal intensive care unit are known to be at particularly high risk for infection due to increased skin permeability, underdeveloped innate and adaptive immune responses, immature mucous membranes, underlying critical illness, and need for frequent invasive procedures [2]. Given both the potential risks and the lack of validation, peri-operative courses have been extended in neonates with only anecdotal evidence of benefit. At our institution, this lack of consensus is demonstrated by inconsistency not only in terms of antimicrobial selection, but also in duration of post-operative administration. Perhaps not surprisingly, this variation in practice is seen throughout North America ([3],[4]).
The potential benefits of a clearly defined peri-operative antibiotic prophylactic dosing regimen include, but are not limited to: decreased antibiotic exposure, limited antibiotic resistance, reduced cost, lower rates of *clostridium difficile* infection, and, most importantly, improved infection rates ([4], [5], [6], [7]). To this end, several groups have adopted adult guidelines for older children undergoing general surgery procedures, administering a preoperative dose of antibiotics followed by a maximum 24-hour postoperative course ([5], [6]). Additionally, two papers have described prophylaxis regimens specific to the neonatal population. First, the Toronto group ([6]) has reviewed available clinical practice guidelines to develop a 48-hour protocol for neonatal colorectal surgery, although this protocol's infection rates have not yet been reported. Similarly, though outside of pediatric general surgery, Columbia has limited perioperative antibiotic administration for neonatal cardiac surgery to 48-hours without increasing infection rates

3. Concise Summary of Project:

This project will have three phases. First, we will determine infection rates for patient in our neonatal intensive care unit undergoing specific Class II and III general surgical procedures, and compare these rates to national averages by reviewing the National Surgical Quality Improvement Program – Pediatric (NSQIP-P) database ([8]). Next, we will examine infection rates for the various peri-operative antibiotic regimes used in our NICU to determine if any one regimen demonstrates superiority. Should none be identified, we will adopt the Toronto group's 48-hour protocol, as it provides both a structured regimen and the additional coverage necessitated by expert opinion. Finally, we will complete the quality improvement

portion of the project. In order to build consensus, we will present our findings to the departments of general surgery, anesthesiology, and neonatology. Next, to facilitate adoption of the regimen, we will develop a standardized antibiotic prophylaxis order set for the EPIC EMR. We will then measure both compliance and infection rates after these interventions, with secondary outcomes to be determined.

4. Study Procedures:

II. Project Plan

1. – Define the problem
    - Quantify the Surgical Site Infection (SSI) rate for class II and III abdominal and non-cardiac thoracic procedures in our NICU within 30 days of operation by reviewing the electronic medical record.
        - NSQIP Neonate definition:
            - Term infant (37 weeks of completed gestation): 28 days of life
            - Preterm infant (less than 37 weeks of completed gestation): 50 weeks post conceptual age
    - Use the NSQIP-P data to compare our rates with national averages.
    - Compare SSI rates between groups treated with different prophylaxis strategies; i.e.:
        - ≤ 24hrs vs. 48hrs vs. >48hrs
        - Appropriate vs. inappropriate antibiotic selection, dosing, and administration time based on SIS/IDSA guidelines:
            - Procedure specific antibiotics
                - Thoracic
                    - Standard
                        - Cefazolin (30mg/kg; Re-dose at 4hours)
                        - Ampicillin-Sulbactam (50mg/kg; Re-dose at 2hours)
                    - β-Lactam Allergy:
                        - Clindamycin (10mg/kg; Re-dose at 6hours)
                        - Vancomycin (15mg/kg; No Re-dose)
                - Gastroduodenal
                    - Standard: Cefazolin (30mg/kg; Re-dose at 4hours)
                    - β-Lactam Allergy:
                        - Clindamycin (10mg/kg; Re-dose at 6hours)
                        - Vancomycin (15mg/kg; No Re-dose) PLUS
                            - Gentamicin (2.5mg/kg; No Re-dose)
                            - Aztreonam (30mg/kg; Re-dose 4hrs)
                            - Fluoroquinolone (10mg/kg; No Re-dose)
                - Biliary Tract
                    - Standard:
                        - Cefazolin (30mg/kg; Re-dose at 4hours)
                        - Cefoxitin (40mg/kg; Re-dose at 2hours)
                        - Cefotetan (40mg/kg; Re-dose at 6hours)
                        - Ceftriaxone (50-75mg/kg; No Re-dose)
                        - Ampicillin-Sulbactam (50mg/kg; Re-dose at 2hours)
                    - β-Lactam Allergy:
                        - Clindamycin (10mg/kg; Re-dose at 6hours)

- Vancomycin (15mg/kg; No Re-dose) PLUS
  - Gentamicin 2.5mg/kg; No Re-dose)
  - Aztreonam (30mg/kg; Re-dose 4hrs)
  - Fluoroquinolone (10mg/kg; No Re-dose)
- Metronidazole (15mg/kg; No Re-dose) PLUS
  - Gentamicin (2.5mg/kg; No Re-dose)
  - Fluoroquinolone (10mg/kg; No Re-dose)

- Small Intestine
  - Non-Obstructed
    - Standard: Cefazolin (30mg/kg; Re-dose at 4hours)
    - β-Lactam Allergy:
      - Clindamycin (10mg/kg; Re-dose at 6hours) PLUS
        - Gentamicin (2.5mg/kg; No Re-dose)
        - Aztreonam (30mg/kg; Re-dose 4hrs)
        - Fluoroquinolone (10mg/kg; No Re-dose)
  - Obstructed
    - Standard:
      - Cefazolin (30mg/kg; Re-dose at 4hours) PLUS
        - Metronidazole (15mg/kg; No Re-dose)
      - Cefoxitin (40mg/kg; Re-dose at 2hours)
      - Cefotetan (40mg/kg; Re-dose at 6hours)
    - β-Lactam Allergy:
      - Metronidazole (15mg/kg; No Re-dose) PLUS
        - Gentamicin (2.5mg/kg; No Re-dose)
        - Fluoroquinolone (10mg/kg; No Re-dose)
- Colorectal
  - Standard:
    - Cefazolin (30mg/kg; Re-dose at 4hours) PLUS
      - Metronidazole (15mg/kg; No Re-dose)
    - Cefoxitin (40mg/kg; Re-dose at 2hours)
    - Cefotetan (40mg/kg; Re-dose at 6hours)
    - Ampicillin-Sulbactam (50mg/kg; Re-dose at 2hours)
    - Ceftriaxone (50-75mg/kg; No Re-dose) PLUS
      - Metronidazole (15mg/kg; No Re-dose)
    - Ertapenem (15mg/kg; No Re-dose)
  - β-Lactam Allergy
    - Clindamycin (10mg/kg; Re-dose at 6hours) PLUS
      - Gentamicin (2.5mg/kg; No Re-dose)
      - Aztreonam (30mg/kg; Re-dose 4hrs)
      - Fluoroquinolone (10mg/kg; No Re-dose)
    - Metronidazole (15mg/kg; No Re-dose) PLUS
      - Gentamicin (2.5mg/kg; No Re-dose)
      - Fluoroquinolone (10mg/kg; No Re-dose)

- Pre-procedural dosing
  - Vancomycin and Fluoroquinolones: 120 minutes prior to incision
  - All other antibiotics listed: within 60 minutes prior to incision
- Vancomycin administration is reasonable as a primary or adjunctive antibiotic for any of the above procedures in patients with known MRSA colonizatioin

- Data collected will include:
  - Age
  - Gender
  - Ethnicity
  - Diagnosis
  - Procedure Performed
  - Wound Classification
  - Date of Surgery
  - Time of initial antibiotic administration
  - Antibiotic(s) selected
  - Antibiotic(s) dose administered
  - Time of incision
  - Time of skin closure
  - Antibiotic Re-dosing (if applicable)
  - Date/Time of final prophylactic antibiotic administration
  - Presence or absence of infection
  - Site of infection
    - Incisional
      - Superficial skin
      - Deep tissue
    - Deep Organ/Space
  - Infection intervention
    - Antibiotic Treatment
    - Superficial Drainage / Local wound care
    - Percutaneous Drainage
    - Re-operation / Debridement
  - Length of Stay

2. – Intervention
   - Grand-rounds presentation to Surgery/NICU/Anesthesia staff regarding above, including APPs
     - recommendation for antibiotic selection
     - recommendation for antibiotic duration
   - EPIC order set with defined regimens and built-in stop dates (i.e., 5 additional doses of second generation cephalosporin with alternatives for allergies/MRSA/etc.)
3. – Measurement
   - 6-12 month observation depending on anticipated numbers based on retrospective review
   - Primary outcomes
     - Change in SSI rate
     - Improvement in adherence to guidelines
       1. Appropriate antibiotic choice
       2. Appropriate duration of antibiotics
   - Possible Secondary outcomes
     - Rates of antibiotic resistance (this will be available in culture data)
     - Allergic reactions (Benadryl/epinephrine admin as surrogate [4] and/or change in antibiotic class)
     - Cost (This could be very challenging)

5. Sub-Study Procedures:

6. Criteria for Inclusion of Subjects:

- Including
    - Gastrostomy tube placement
    - Ostomy reversal
    - Bowel resection with primary anastomosis or ostomy creation
        1. Atresia, meconium ileus, malrotation (with appendectomy), duplication cyst
    - Hirschprung's pull-through
    - PSARP?

7. Criteria for Exclusion of Subjects:

- Excluding
    - Hernia/hydrocele/circumcision (Class I)
    - NEC/SIP (Class IV)

8. Sources of Research Material:

EPIC Electronic Health Records

9. Recruitment Methods and Consenting Process:

10. Potential Risks:

There are no risks to any patients from this study. All of the antibiotic regimes are considered standard of care. There is a slight risk of allergic reaction to an antibiotic in a neonate. Should this happen, the child will be treated supportively and switched to an appropriate substitute.

11. Subject Safety and Data Monitoring:

There are no risks to any patients from this study

12. Procedures to Maintain Confidentiality:

All information obtained through the medical records will be seen only by the principle investigators, the physicians undertaking this project, and by the research coordinators. Identifiers will be destroyed immediately after data collection is complete. The data collected will be on a password protected computer and all paper documents will be kept in locked cabinets in the research coordinator's office. Only a statistical summary will be publicly reported, divulging no information in the final report that could be linked to a specific patient participating in the study. Identifiers will be destroyed upon completion of the study.

13. Potential Benefits:

There will be no immediate benefit to the patient from this study. We hope that by competing the study, we will have an appropriate antibiotic regime identified and implemented decreasing SSI and concomitant injury.

14. Biostatistics: Data will be analyzed using the SPSS version 18.0. Descriptive statistics will be calculated for the data collected as means, median and standard deviation.

References:

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2. Hooven, T.A. and R.A. Polin, *Healthcare-associated infections in the hospitalized neonate: a review.* Early Hum Dev, 2014. **90 Suppl 1**: p. S4-6.
3. Bucher, B.T., B.W. Warner, and P.A. Dillon, *Antibiotic prophylaxis and the prevention of surgical site infection.* Curr Opin Pediatr, 2011. **23**(3): p. 334-8.
4. Rangel, S.J., et al., *Recent trends in the use of antibiotic prophylaxis in pediatric surgery.* J Pediatr Surg, 2011. **46**(2): p. 366-71.
5. Toltzis, P., et al., *A statewide collaborative to reduce pediatric surgical site infections.* Pediatrics, 2014. **134**(4): p. e1174-80.
6. Khoshbin, A., et al., *Antibiotic Prophylaxis to Prevent Surgical Site Infections in Children: A Prospective Cohort Study.* Ann Surg, 2015. **262**(2): p. 397-402.
7. Murray, M.T., et al., *Implementing a standardized perioperative antibiotic prophylaxis protocol for neonates undergoing cardiac surgery.* Ann Thorac Surg, 2014. **98**(3): p. 927-33.
8. Bruny, J.L., et al., *American College of Surgeons National Surgical Quality Improvement Program Pediatric: a beta phase report.* J Pediatr Surg, 2013. **48**(1): p. 74-80.